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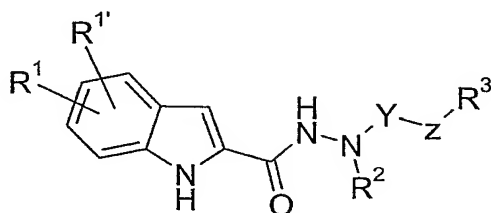
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(54) Title: **INDOLE-2-CARBOXYLIC ACID HYDRAZIDES**



(I)

(57) Abstract: Compounds of formula (I) or pharmaceutically acceptable salts thereof, are inhibitors of glycogen phosphorylase and are useful in the prophylactic or therapeutic treatment of diabetes, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia, e.g. myocardial ischemia, or as cardioprotectants or inhibitors of abnormal cell growth.



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TITLE OF THE INVENTION

INDOLE-2-CARBOXYLIC ACID HYDRAZIDES

BACKGROUND OF THE INVENTION

The present invention is directed to indole-2-carboxylic acid hydrazides. In particular, the present invention is directed to indole-2-carboxylic acid hydrazides that are inhibitors of glycogen phosphorylase.

Insulin dependent Type I diabetes and non-insulin dependent Type II diabetes continue to present treatment difficulties even though clinically accepted regimens that include diet, exercise, hypoglycemic agents, and insulin are available. Treatment is patient dependent, therefore there is a continuing need for novel hypoglycemic agents, particularly ones that may be better tolerated with fewer adverse effects.

The liver and certain other organs produce glucose (thereby raising the blood sugar level) by breaking down glycogen or by synthesizing glucose from small molecule precursors. The breakdown of glycogen is catalyzed by glycogen phosphorylase enzyme. Accordingly, inhibiting glycogen phosphorylase ("GP") may lower the elevated blood sugar level in diabetic patients.

Similarly, hypertension and its associated pathologies such as, for example, atherosclerosis, lipidemia, hyperlipidemia and hypercholesterolemia have been associated with elevated insulin levels (hyperinsulinemia), which can lead to abnormal blood sugar levels. Furthermore, myocardial ischemia can result. Such maladies may be treated with hypoglycemic agents, including compounds that inhibit glycogen phosphorylase. Accordingly, it is accepted that compounds that inhibit glycogen phosphorylase (see, for example, U.S. Patent No. 6,297,269) are useful in the treatment of diabetes, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, atherosclerosis or myocardial ischemia. Nevertheless, it would be desirable to obtain other novel compounds that inhibit glycogen phosphorylase.

R. Kurukulasuriya, J.T. Link, et al., *Current Medicinal Chem.*, 10:99-121(2003) describes "Prospects for Pharmacologic Inhibition of Hepatic Glucose Production." R. Kurukulasuriya, J.T. Link, et al., *Current Medicinal Chem.*, 10:123-153(2003) describes "Potential Drug Targets and Progress Towards Pharmacologic Inhibition of Hepatic Glucose Production."

U.S. Patent No. 6,297,269 and European Patent No. EP 0832066 describe substituted *N*-(indole-2-carbonyl)amides and derivatives as glycogen phosphorylase inhibitors. U.S. Patent Nos. 6,107,329 and 6,277,877 describe substituted *N*-(indole-2-carbonyl)glycinamides and derivatives as glycogen phosphorylase inhibitors. U.S. Patent No. 6,399,601 describes bicyclic pyrrolyl amides as glycogen phosphorylase inhibitors. International Patent Publication No. WO 03/037864 describes indole derivatives as glycogen phosphorylase inhibitors. European Patent Application No. EP 0978276 and EP 1136071 describe inhibitors of human glycogen phosphorylase and their use. International Patent Publication No. WO 01/68055 describes glycogen phosphorylase inhibitors. U.S. Patent No. 5,952,322 describes a method of reducing non-cardiac ischemial tissue damage using glycogen phosphorylase inhibitors.

European Patent Application No. EP1177791 describes the use of glycogen phosphorylase inhibitors to inhibit abnormal cell growth, e.g. in the treatment of cancer and hyperproliferative disorders.

International Patent Publication No. WO 04/104001 (published after the priority date of the present application) discloses pyrrolopyridine-2-carboxylic acid amide inhibitors of glycogen phosphorylase.

International Patent Publication No. WO 04/113345 (published after the priority date of the present application) discloses fused pyrrole compounds as inhibitors of glycogen phosphorylase.

International Patent Publication No. WO 01/55146 describes arylamidines. International Patent Publication No. WO 01/62775 describes antiarrhythmic peptides. International Patent Publication No. WO 01/96346 describes tricyclic compounds. International Patent Publication No. WO 02/16314 describes substituted polyamine compounds. International Patent Publication No. WO 02/20475 describes serine protease activity inhibitors. International Patent Publication No. WO 02/40469 describes bombesin receptor antagonists. International Patent Publication No. WO 02/46159 describes guanidine and amidine derivatives. International Patent Publication No. WO 00/69815 describes ureido-substituted cyclic amine derivatives.

International Patent Publication No. WO 00/43384 describes aromatic heterocyclic compounds. International Patent Publication Nos. WO 02/26697 and WO 00/76970 describe aromatic derivatives. International Patent Publication No. WO 01/32622 describes indoles. European Patent Application No. EP 1101759 describes phenylazole compounds. European Patent Application No. EP 1179341 describes cyclic amino compounds. U.S. Patent No. 6,037,325 describes substituted heterocyclic compounds. U.S. Patent No. 5,672,582 describes 4-substituted cyclohexylamine derivatives. European Patent Application No. EP 1201239 describes cyclic amine CCR3 antagonists. International Patent Publication No. WO 98/25617 describes substituted arylpiperazines. U.S. Patent No. 5,756,810 describes preparing 3-nitro benzoate compounds.

U.S. Patent No. 5,710,153 describes tetrazole compounds. U.S. Patent Nos. 6,174,887 and 6,420,561 describe amide compounds. S.P. Hiremath et al., *Acta Ciencia Indica*, XVIII:397(1992) describes the synthesis and biological activities of indolylthiosemicarbazides and semicarbazides. International Patent Publication No. WO 96/36595 describes 3,4-disubstituted phenylsulphonamides. U.S. Patent No. 5,618,825 describes combinatorial sulfonamide libraries. European Patent Application No. EP 0810221 describes oxygen-containing heterocyclic derivatives. European Patent Application No. 0345990 describes polypeptide compounds. European Patent Application No. 0254545 describes diamine compounds.

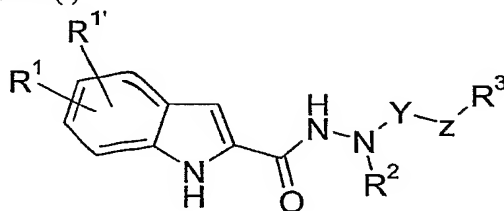
International Patent Publication No. WO 97/31016 describes inhibitors of SH2-mediated processes. U.S. Patent No. 6,034,067 describes serine protease inhibitors. International Patent Publication No. WO 97/17985 and U.S. Patent No. 6,107,309 describe hemoregulatory compounds. U.S. Patent No. 6,432,921 describes thrombin inhibitors. U.K. Patent Application No. GB 2292149 describes peptide inhibitors of pro-interleukin-1 β converting enzyme. U.S. Patent No. 5,821,241 describes fibrinogen receptor antagonists.

International Patent Publication No. WO 01/02424 describes peptide boronic acid compounds. U.S. Patent Nos. 6,001,811, 5,869,455 and 5,618,792 describe oxadiazole, thiadiazole and triazole peptoids. U.S. Patent Nos. 5,885,967, 6,090,787 and 6,124,277 describe thrombin inhibiting peptide derivatives. U.S. Patent No. 6,455,529 describes adhesion receptor antagonists. U.S. Patent No. 6,410,684 describes serine protease inhibitors.

International Patent Publication No. WO 01/94310 describes bis-heterocyclic alkaloids. U.S. Patent Publication No. 20030004162A1, European Patent Application No. EP 0846464 and International Patent Publication No. WO 96/39384 describe glycogen phosphorylase inhibitors. International Patent Publication No. WO 97/28798 describes pyrrolidine derivatives. U.S. Patent No. 5,346,907 describes amino acid analogs.

SUMMARY OF THE INVENTION

Compounds of formula (I):

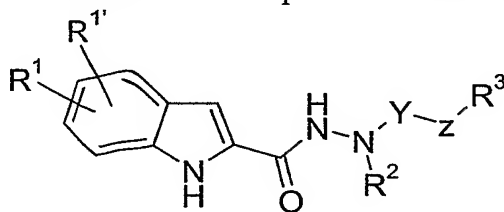


I

or pharmaceutically acceptable salts thereof, are inhibitors of glycogen phosphorylase and are useful in the prophylactic or therapeutic treatment of diabetes, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia e.g. myocardial ischemia, or as cardioprotectants or inhibitors of abnormal cell proliferation.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a compound of formula (I):



I

or a pharmaceutically acceptable salt thereof, wherein:

Y is -C(O)-, -S(O)₂-, or -C(NH)-;

Z is C₁₋₄alkylene, oxygen, -(CH₂)_mO-, -O(CH₂)_m-, -NR-, -(CH₂)_mNR-, -NR(CH₂)_m-, -(CH₂)_mS(O)₂-, or a bond;

m is 1, 2, 3, or 4;

R is C₀₋₄alkyl, C₀₋₄alkylaryl, or C₀₋₄alkylheoaryl;

R¹ and R^{1'} are each independently, halogen, hydroxy, cyano, C₀₋₄alkyl, C₁₋₄alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, ethenyl, or ethynyl;

R^2 is C_{0-4} alkyl, $COOR^6$, COR^6 , $C_{1-4}alkoxyC_{1-4}alkyl-$, hydroxy $C_{1-4}alkyl-$, cycloalkyl $C_{0-4}alkyl-$, aryl $C_{0-4}alkyl-$, or hetaryl $C_{0-4}alkyl-$, wherein any of the aryl or hetaryl rings are optionally substituted with 1-2 independent halogen, cyano, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-SO_2C_{1-4}alkyl$, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents;

R^3 is hydrogen, $-COOC_{0-4}alkyl$, $C_{1-4}alkoxy$, $C_{1-4}alkyl$, aryl $C_{1-4}alkylthio-$, $-C_{0-4}alkylaryl$, $-C_{0-4}alkylhetaryl$, $-C_{0-4}alkylcycloalkyl$, or $-C_{0-4}alkylheterocyclyl$, wherein any of the rings is optionally substituted with 1-3 independent halogen, cyano, $C_{1-4}alkyl$, fluoromethyl, difluoromethyl, trifluoromethyl, $-C_{0-4}alkylNHC(O)O(C_{1-4}alkyl)$, $-C_{0-4}alkylNR^7R^8$, $-C(O)R^9$, $C_{1-4}alkoxyC_{0-4}alkyl-$, $-COOC_{0-4}alkyl$, $-C_{0-4}alkylNHC(O)R^9$, $-C_{0-4}alkylC(O)N(R^{10})_2$, $-C_{1-4}alkoxyC_{1-4}alkoxy$, hydroxy $C_{0-4}alkyl-$, $-NHSO_2R^{10}$, $-SO_2(C_{1-4}alkyl)$, $-SO_2NR^{11}R^{12}$, 5- to 6-membered heterocyclyl, phenyl $C_{0-2}alkoxy$, or phenyl $C_{0-2}alkyl$ substituents, wherein phenyl is optionally substituted with 1-2 independent halogen, cyano, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $-SO_2C_{1-4}alkyl$, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents, or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo ($=O$) substituent;

or R^3 is $-NR^4(-C_{0-4}alkylR^5)$;

R^4 is $C_{0-3}alkyl$, $-C_{2-3}alkyl-NR^7R^8$, $C_{3-6}cycloalkyl$ optionally substituted by hydroxy $C_{0-4}alkyl-$ further optionally substituted by hydroxy, $C_{1-2}alkoxyC_{2-4}alkyl-$, or $C_{1-2}alkyl-S(O)_n-C_{2-3}alkyl-$;

n is 0, 1, or 2;

R^5 is hydrogen, hydroxy $C_{2-3}alkyl-$, $C_{1-2}alkoxyC_{0-4}alkyl-$, or aryl, hetaryl, or heterocyclyl;

wherein a heterocyclic nitrogen-containing R^5 ring optionally is mono-substituted on the ring nitrogen with $C_{1-4}alkyl$, benzyl, benzoyl, $C_{1-4}alkyl-C(O)-$, $-SO_2C_{1-4}alkyl$, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, $C_{1-4}alkoxycarbonyl$, or aryl($C_{1-4}alkoxy$)carbonyl; and wherein the R^5 rings are optionally mono-substituted on a ring carbon with halogen, cyano, $C_{1-4}alkyl-C(O)-$, $C_{1-4}alkyl-SO_2-$, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, hydroxy, $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$, hydroxy $C_{0-4}alkyl-$, or $C_{0-4}alkylcarbamoyl-$, provided that no quaternised nitrogen is included; or two bonds on a ring carbon of the heterocycle optionally can form an oxo ($=O$) substituent;

R^6 is $C_{1-4}alkyl$, aryl, or hetaryl;

R^7 and R^8 are independently $C_{0-4}alkyl$, $C_{3-6}cycloalkyl$, or $CO(C_{1-4}alkyl)$;

R^9 is $C_{1-4}alkyl$, or $C_{3-6}cycloalkyl$;

R^{10} is $C_{0-4}alkyl$, or $C_{3-6}cycloalkyl$; and

R^{11} and R^{12} are independently $C_{0-4}alkyl$ or together with the nitrogen to which they are attached may form a 4- to 6-membered heterocycle;

provided there are no nitrogen-oxygen, nitrogen-nitrogen, oxygen-oxygen or nitrogen-halogen bonds in the grouping $-Y-Z-R^3$; and

provided that when $-Y-Z-$ represents $-C(O)-$, $-C(NH)-$, $-C(O)-C_{1-4}alkylene$, $-C(NH)-C_{1-4}alkylene$, $-C(O)-NR-$, $-C(NH)-NR-$, $-C(O)-(CH_2)_mNR-$, or $-C(NH)-(CH_2)_mNR-$, then R^3 is not optionally substituted $C_{3-10}cycloalkyl$, $C_{5-10}cycloalkenyl$, phenyl, naphthyl, pyridyl, pyrazinyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, furanyl, thiophenyl, pyrrolyl, pyrrolidinyl, piperidinyl, indolyl, benzo[1,3]dioxol, thieno[2,3-b]pyrrolyl, or thieno[3,2-b]pyrrolyl.

The molecular weight of the compounds of formula (I) is preferably less than 800, more preferably less than 600.

Y is preferably -C(O)- or -S(O)₂-.

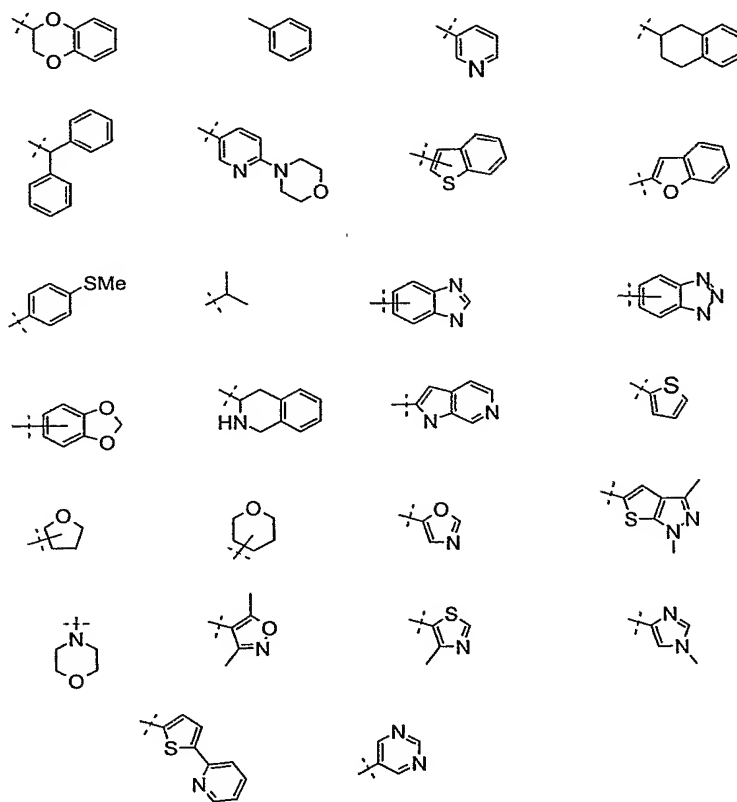
Z is preferably a C₁₋₄alkylene, oxygen, -(CH₂)_mO-, -NR- or a bond. More preferably Z is a bond.

R is preferably C₀₋₄alkyl.

R¹ and R^{1'} are preferably each independently, hydrogen, halogen or cyano. More preferably one of R¹ and R^{1'} is hydrogen and the other is halogen, e.g. chloro. More preferably one of R¹ and R^{1'} is hydrogen and the other is 5-chloro.

R² is preferably C₀₋₄alkyl. More preferably R² is hydrogen.

Specific groups which R³ may represent include the following:



wherein any of the rings is optionally substituted by up to 3 substituents as described above for R³.

Further specific R³ groups include those present in the Examples.

Specific compounds of the invention which may be mentioned are those included in the Examples and pharmaceutically acceptable salts thereof.

While the preferred groups for each variable have generally been listed above separately for each variable, preferred compounds of this invention include those in which several or each variable in formula (I) is selected from the preferred, more preferred, most preferred, especially or particularly listed groups for each variable. Therefore, this invention is intended to include

all combinations of preferred, more preferred, most preferred, especially and particularly listed groups.

As used herein, unless stated otherwise, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkenyl, alkynyl, and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains having at least one unsaturated carbon-carbon bond.

As used herein, for example, "C₀₋₄alkyl" is used to mean an alkyl having 0-4 carbons – that is, 0, 1, 2, 3, or 4 carbons in a straight or branched configuration. An alkyl having no carbon is hydrogen when the alkyl is a terminal group. An alkyl having no carbon is a direct bond when the alkyl is a bridging (connecting) group.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and include mono-, bi-, and tricyclic saturated carbocycles, as well as fused and bridged systems. Such fused ring systems can include one ring that is partially or fully unsaturated, such as a benzene ring, to form fused ring systems, such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl and carbocyclic rings include C₃₋₁₀cycloalkyl, e.g. C₃₋₈cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and decahydronaphthalene, adamantane, indanyl, 1,2,3,4-tetrahydronaphthalene and the like.

The term "halogen" includes fluorine, chlorine, bromine, and iodine atoms.

The term "aryl" is well known to chemists. The preferred aryl groups are phenyl and naphthyl, especially phenyl.

The term "hetaryl" is well known to chemists. The term includes 5- or 6-membered heteroaryl rings containing 1–4 heteroatoms chosen from oxygen, sulfur, and nitrogen in which oxygen and sulfur are not next to each other. Examples of such heteroaryl rings are furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. The term "hetaryl" includes hetaryl rings with fused carbocyclic ring systems that are partially or fully unsaturated, such as a benzene ring, to form a benzofused hetaryl. For example, benzimidazole, benzoxazole, benzothiazole, benzofuran, quinoline, isoquinoline, quinoxaline, and the like.

Unless otherwise stated, the terms "heterocyclic ring" and "heterocyclyl" are equivalent, and include 4–8-membered saturated or partially saturated rings containing one or two heteroatoms chosen from oxygen, sulfur, and nitrogen. The sulfur and oxygen heteroatoms are not directly attached to one another. Any nitrogen heteroatoms in the ring may optionally be substituted with C₁₋₄alkyl. Examples of heterocyclic rings include azetidine, oxetane, tetrahydrofuran, tetrahydropyran, oxepane, oxocane, thietane, thiazolidine, oxazolidine, oxazetidine, pyrazolidine, isoxazolidine, isothiazolidine, tetrahydrothiophene, tetrahydrothiopyran, thiepane, thiocane, azetidine, pyrrolidine, piperidine, *N*-methylpiperidine, azepane, azocane, [1,3]dioxane, oxazolidine, piperazine, homopiperazine, morpholine, thiomorpholine, 1,2,3,6-tetrahydropyridine and the like. Other examples of heterocyclic rings include the oxidized forms of the sulfur-containing rings. Thus, tetrahydrothiophene-1-oxide, tetrahydrothiophene-1,1-dioxide, thiomorpholine-1-oxide, thiomorpholine-1,1-dioxide,

tetrahydrothiopyran-1-oxide, tetrahydrothiopyran-1,1-dioxide, thiazolidine-1-oxide, and thiazolidine-1,1-dioxide are also considered to be heterocyclic rings. The term "heterocyclic" also includes fused ring systems and can include a carbocyclic ring that is partially or fully unsaturated, such as a benzene ring, to form benzofused heterocycles. For example, 3,4-dihydro-1,4-benzodioxine, tetrahydroquinoline, tetrahydroisoquinoline and the like.

Compounds described herein may contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above formula (I) is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of formula (I) and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

When a tautomer of the compound of the formula (I) exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically drawn or stated otherwise.

When the compound of formula (I) and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

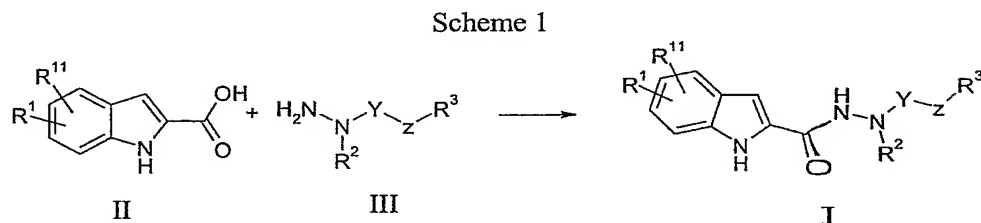
The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include arginine, betaine, caffeine, choline, *N,N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric,

isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like

Since the compounds of formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure especially at least 98% pure (% are on a weight for weight basis).

The compounds of formula (I) can be prepared as outlined in Scheme 1 below wherein R^1 , $R^{1'}$, R^2 , R^3 , Y and Z are as defined above for formula (I):



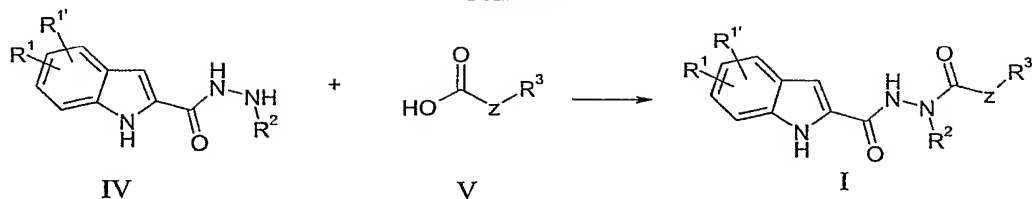
According to Scheme 1, the compounds of formula (I) may be prepared by coupling the appropriate indole-2-carboxylic acid of formula (II) with the appropriate hydrazide of formula (III), wherein $Y = C(O)$. Compounds of formula (II) and compounds of formula (III) are generally commercially available or are readily prepared by known techniques.

Typically, the compound of formula (II) is combined with compounds of formula (III) in the presence of a suitable coupling agent. Examples of suitable coupling reagents are 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride/hydroxybenzotriazole (EDCI / HOBt), 1,1-carbonyldiimidazole (CDI), dicyclohexylcarbodiimide/hydroxybenzotriazole (DCC / HOBt), *O*-(1H-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (R. Knorr *et al.*, *Tetrahedron Lett.*, **1989**, *30*, 1927) and polymer supported carbodiimide-1-hydroxybenzotriazole (for representative procedures, see for example, Argonaut Technical Note 501 available from Argonaut Technologies, Inc., Foster City, California).

The couplings are performed in an inert solvent, preferably an aprotic solvent at a temperature of about 0°C to about 45°C for about 1 to 72h in the presence of a tertiary amine base such as diisopropylethylamine (DIPEA) or triethylamine. Exemplary solvents include acetonitrile, chloroform, dichloromethane, *N,N*-dimethylformamide (DMF) or mixtures thereof. Use of these coupling agents and appropriate selection of solvents and temperatures are known to those skilled in the art or can be readily determined from the literature. These and other exemplary conditions useful for coupling carboxylic acids are described in Houben-Weyl, Vol XV, part II, E. Wunsch, Ed., G. Thieme Verlag, 1974, Stuttgart, and M. Bodansky, Principles of Peptide Synthesis, Springer-Verlag, Berlin, 1984 and The Peptides, Analysis, Synthesis and Biology (Ed., E. Gross and J. Meienhofer), Vols 1-5, Academic Press NY 1979-1983.

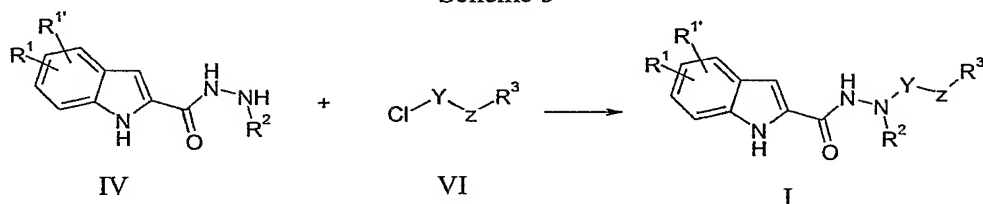
The compounds of formula (I), wherein Y is $C=O$, may be prepared according to Scheme 2 by coupling the appropriate hydrazide of formula (IV) with the appropriate carboxylic acid of formula (V). Examples of suitable coupling agents and conditions are as described above. Compounds of formula (IV) can be obtained by the synthesis described in Scheme 7 below. Compounds of formula (V) are commercially available or are readily prepared by known techniques.

Scheme 2



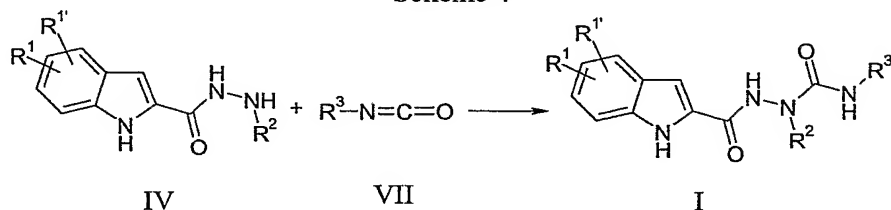
The compounds of formula (I), wherein Y is C(O) or -SO₂-, may also be prepared according to Scheme 3 by mixing the appropriate hydrazide of formula (IV) with the appropriate acid chloride or sulfonyl chloride of formula (VI) in pyridine at room temperature, or alternatively in the presence of a tertiary amine base, e.g. diisopropylethylamine in a solvent such as 1,4-dioxane or THF at room temperature. Acid chlorides or sulfonyl chlorides of formula (VI) are commercially available or are readily prepared by known techniques.

Scheme 3



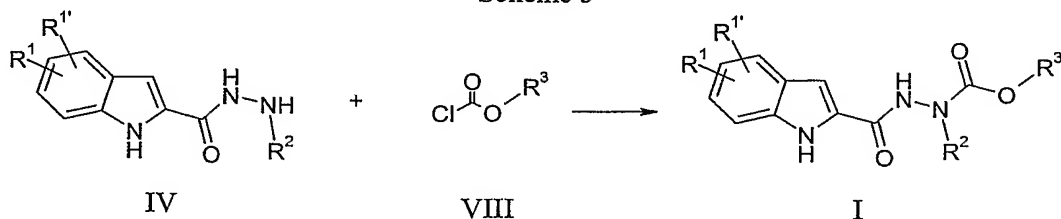
The compounds of formula (I), wherein Y is C(O) and Z is NH, may be prepared according to Scheme 4 by heating the appropriate hydrazide of formula (IV) with the appropriate isocyanate of formula (VII) under reflux in the presence of a tertiary amine base, e.g. diisopropylethylamine in a solvent such as 1,4-dioxane or toluene.

Scheme 4



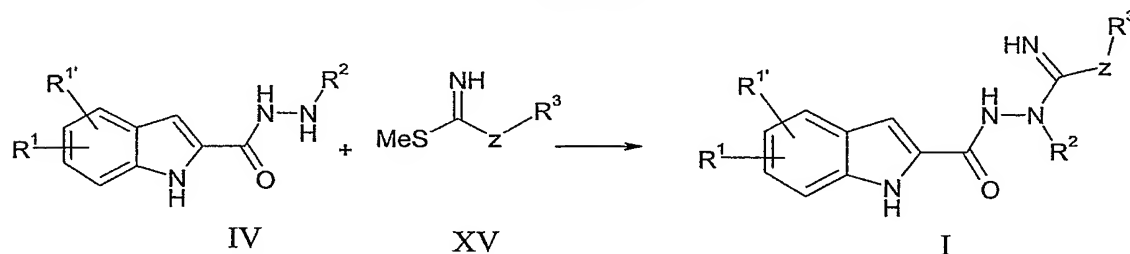
The compounds of formula (I), wherein Y is C(O) and Z is oxygen, may be prepared according to Scheme 5 by mixing the appropriate hydrazide of formula (IV) with the appropriate chloroformate of formula (VIII) in the presence of a tertiary amine base, e.g. triethylamine in a solvent such as dichloromethane.

Scheme 5



The compounds of formula (I), wherein Y is C(NH), may be prepared according to Scheme 6 by mixing the appropriate hydrazide of formula (IV) with the appropriate thioimide of formula (XV) in a solvent such as ethanol or dimethylformamide.

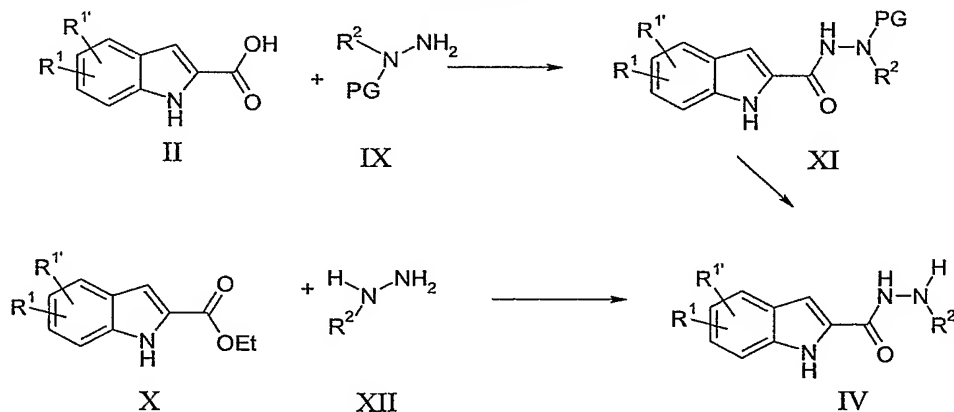
Scheme 6



Formula (XI) compounds may be prepared as described in Scheme 7 by coupling of carboxylic acids of formula (II) with hydrazines of formula (IX), wherein PG is a protecting group, e.g. Boc. Examples of suitable coupling agents and conditions are as described above. Formula (IV) compounds may then be prepared by removal of the protecting group, e.g. where PG is Boc, under acidic conditions using for example trifluoroacetic acid in dichloromethane at temperatures of around 25°C. Formula (II) compounds are commercially available or are readily prepared by known techniques. Formula (IX) compounds are commercially available or are readily prepared by known techniques.

Alternatively compounds of formula (IV), wherein R² is hydrogen, may be prepared (Scheme 7) by heating an ethyl ester of formula (X) with compounds of formula (XII), wherein R² is hydrogen, in a solvent such as ethanol under reflux for a period of 3 to 24h.

Scheme 7



Further details for the preparation of the compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds and more preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial "split and mix" approach or by multiple parallel synthesis using either solution or solid phase chemistry, using procedures known to those skilled in the art.

During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The

compounds of formulae (II) and (IV) may be protected in the 1-position e.g. with an arylmethyl, acyl, alkoxycarbonyl, sulfonyl or silyl group. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in for example, *Protective Groups in Organic Chemistry*, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2nd edition.

Any novel intermediates as defined above are also included within the scope of the invention.

As indicated above the compounds of formula (I) are useful as inhibitors of glycogen phosphorylase, for the treatment of conditions such as diabetes, particularly Type II diabetes. For such use the compounds of formula (I) will generally be administered in the form of a pharmaceutical composition.

The invention also encompasses a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Moreover, the invention also provides a pharmaceutical composition for the treatment of disease by inhibiting glycogen phosphorylase, resulting in the prophylactic or therapeutic treatment of diabetes, hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia, e.g. myocardial ischemia, cardioprotection or inhibition of abnormal cell growth, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula (I), or a pharmaceutically acceptable salt thereof.

The pharmaceutical compositions may optionally comprise other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds of formula (I), or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous).

Thus, the pharmaceutical compositions can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound of formula (I), or a pharmaceutically acceptable salt thereof, may also be

administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient.

For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or

dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, using a compound of formula (I), or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of formula (I), or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, diabetes and hyperglycemia may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Similarly, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, atherosclerosis or myocardial ischemia may be effectively treated, or cardioprotection or inhibition of abnormal cell growth achieved, by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of formula (I) may be used in the treatment of diseases or conditions in which glycogen phosphorylase plays a role.

Thus the invention also provides a method for the treatment of a disease or condition in which glycogen phosphorylase plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Diseases or conditions in which glycogen phosphorylase plays a role include diabetes (including Type I and Type II, impaired glucose tolerance, insulin resistance and diabetic complications such as neuropathy, nephropathy, retinopathy and cataracts), hyperglycemia, hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis, tissue ischemia e.g. myocardial ischemia, cardioprotection and abnormal cell growth e.g. cancer or hyperproliferative disorders.

The invention also provides a method for the treatment of hyperglycemia or diabetes, particularly Type II diabetes, comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the prevention of diabetes in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance comprising a step of administering to a subject in need thereof an effective prophylactic amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In the treatment of diabetes, e.g. Type II diabetes, the compounds of the invention are particularly suited to night time dosing, optionally in combination with another antidiabetic agent.

The invention also provides a method for the treatment of hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia, or achieving cardioprotection or inhibition of abnormal cell growth, comprising a step of administering to a patient in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the treatment of a condition as defined above.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition as defined above.

In the methods of the invention the term "treatment" includes both therapeutic and prophylactic treatment.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, may be administered alone or in combination with one or more other therapeutically active compounds. The other therapeutically active compounds may be for the treatment of the same disease or condition as the compounds of formula (I) or a different disease or condition. The therapeutically active compounds may be administered simultaneously, sequentially or separately.

The compounds of Formula (I) may be administered with other active compounds for the treatment of diabetes, for example insulin and insulin analogs, sulfonyl ureas and analogs, biguanides, α_2 agonists, fatty acid oxidation inhibitors, α -glucosidase inhibitors, β -agonists, phosphodiesterase inhibitors, lipid lowering agents, antiobesity agents, amylin antagonists, lipoxigenase inhibitors, somostatin analogs, glucokinase activators, glucagon antagonists, insulin signalling agonists, PTP1B inhibitors, gluconeogenesis inhibitors, antilypolytic agents, GSK inhibitors, galanin receptor agonists, anorectic agents, CCK receptor agonists, leptin, CRF antagonists or CRF binding proteins.

The compounds of formula (I) may also be administered in combination with thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors or sorbitol dehydrogenase inhibitors.

All publications, including, but not limited to, patents and patent application cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as fully set forth.

The invention will now be described by reference to the following examples which are for illustrative purposes and are not to be construed as a limitation of the scope of the present invention.

EXAMPLES

Materials & methods:

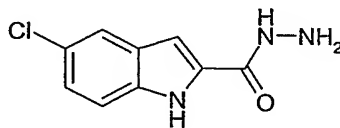
Column chromatography was carried out on SiO₂ (40–63 mesh). LCMS data were obtained using a Waters Symmetry 3.5 μ C₁₈ column (2.1 \times 30.0 mm, flow rate = 0.8 mL min⁻¹) eluting with a (5% MeCN in H₂O)–MeCN solution containing 0.1% HCO₂H over 6min & UV detection at 220nm. Gradient information: 0.0–1.2min: 100% (5% MeCN in H₂O); 1.2–3.8min: Ramp up to 10% (5% MeCN in H₂O)–90% MeCN; 3.8–4.4min: Hold at 10% (5% MeCN in H₂O)–90% MeCN; 4.4–5.5min: Ramp up to 100% MeCN; 5.5–6.0min: Return to 100% (5% MeCN in H₂O). The mass spectra were obtained employing an electrospray ionisation source in the positive (ES⁺) ion mode. Mass directed purification was performed on a Micromass Platform LC with cone voltage 30v, employing an electrospray ionisation source in the positive (ES⁺) ion mode, Waters 996 Photodiode Array Detector (210–390nm), Xterra Prep MS, C₁₈, 5 μ 19x50mm columns, and a mobile Phase of MeCN + 0.1% Formic Acid / H₂O+5%MeCN+0.1% Formic Acid. NMR spectra were acquired at 27°C on a Varian Mercury 400 spectrometer operating at 400 MHz or on a Bruker AMX2 500 spectrometer operating at 500MHz.

Abbreviations & acronyms:

CDI: 1,1-carbonyldiimidazole; DCM: dichloromethane; DIPEA: *N,N*-Diisopropylethylamine; DMF: *N,N*-Dimethylformamide; DMSO: Dimethylsulfoxide; EDCI: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; GP: Glycogen Phosphorylase; Glc: Glucose; G6P: Glucose-6-phosphate; G6PDH: Glucose-6-phosphate dehydrogenase; HATU: *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; HOBt: 1-Hydroxybenzotriazole; MgSO₄: magnesium sulfate; PS: Polymer supported; rt: room temperature; RT: Retention time; THF: Tetrahydrofuran.

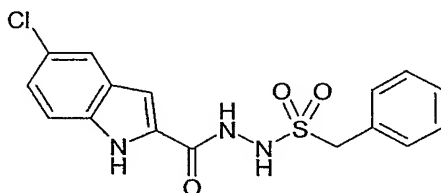
INTERMEDIATES

Preparation 1: 5-Chloroindole-2-carboxylic acid hydrazide



This compound was prepared according to the method of Musser and Brown (*J. Med. Chem.*, 1984, 27, 121).

EXAMPLE 1

5-Chloro-1*H*-indole-2-carboxylic acid *N'*-(phenylmethanesulfonyl)hydrazide

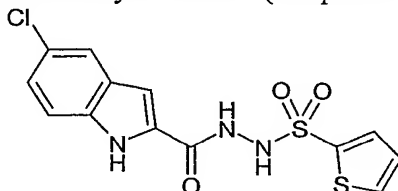
To a solution of 5-chloro-1*H*-indole-2-carboxylic acid hydrazide (Preparation 1, 100mg, 0.48mmol) in 1,4-dioxane (5mL) was added phenylmethanesulfonyl chloride (91mg, 0.48mmol) and DIPEA (83μL, 0.48mmol) and the mixture was stirred at rt for 16h. After concentration *in vacuo*, the residue was redissolved in ethyl acetate (200mL) and successively washed with hydrochloric acid (1N, 50mL), sodium hydroxide solution (1N, 50mL) and brine (50mL). The organic layer was dried (MgSO₄) and concentrated *in vacuo* to give the title compound as a colourless solid. m/z (ES⁺) = 364 [$M + 1$]⁺; RT = 3.58min.

The coupling of 5-chloroindole-2-carboxylic acid hydrazide with sulfonyl chlorides, outlined in EXAMPLE 1, was also employed to prepare the compounds listed in Table 1 below.

Table 1

| EX. | Structure | Name | RT(min) | m/z (ES ⁺) |
|-----|-----------|---|---------|--------------------------|
| 2 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -(5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl)hydrazide | 4.03 | 455 |
| 3 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -(propyl-2-sulfonyl)hydrazide | 3.36 | 316 |
| 4 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -(butyl-1-sulfonyl)hydrazide | 1.51 | 330 |

EXAMPLE 5

5-Chloro-1*H*-indole-2-carboxylic acid *N'*-(thiophene-2-sulfonyl) hydrazide

To a solution of 5-chloro-1*H*-indole-2-carboxylic acid hydrazide (Preparation 1, 100mg, 0.48mmol) in pyridine (5mL), was added thiophene-2-sulfonyl chloride (87 mg, 0.48mmol). The reaction mixture was stirred for 16h at rt. Addition of water (15mL) gave a white precipitate that was collected by filtration and recrystallised from ethanol to give the title compound. m/z (ES^+) = 356 [$M + H$] $^+$; RT = 3.50min.

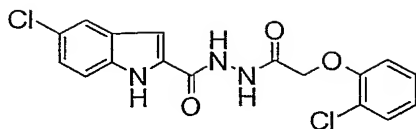
The procedure exemplified by the preparation of EXAMPLE 5 was also used to prepare the sulfonyl hydrazides shown in Table 2.

Table 2

| EX. | Structure | Name | RT(min) | m/z (ES^+) |
|-----|-----------|--|---------|------------------|
| 6 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -(3-5-dimethylisoxazole-4-sulfonyl)hydrazide | 3.55 | 369 |
| 7 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -(2-acetylamino-4-methylthiazole-5-sulfonyl)hydrazide | 3.23 | 428 |
| 8 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -(1-methyl-1 <i>H</i> -imidazole-4-sulfonyl)hydrazide | 3.07 | 354 |
| 9 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -(4-pyridin-2-ylthiophene-2-sulfonyl)hydrazide | 3.73 | 433 |
| 10 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -(4-chloropyridine-3-sulfonyl)hydrazide | 3.29 | 385 |
| 11 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -(3-methoxy-4-(methoxycarbonyl)thiophene-2-sulfonyl)hydrazide | 3.65 | 444 |

EXAMPLE 12

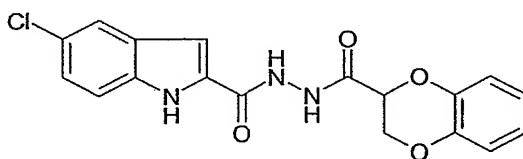
5-Chloro-1*H*-indole-2-carboxylic acid *N'*-[(2-chlorophenoxy)acetyl]hydrazide



To a solution of 5-chloro-1*H*-indole-2-carboxylic acid (0.2g, 1mmol) in DCM (10mL) was added DIPEA (0.38mL, 2.2mmol), HOBT (0.2g, 1.5mmol), and 2-chlorophenoxyacetic acid hydrazide (0.2g, 1.0mmol). After 5min, EDCI (63mg, 0.33mmol) was added and the reaction mixture was stirred at rt for 72h. The title compound was collected by filtration. m/z (ES^+) = 379 [$M + H$] $^+$; RT = 1.76min.

EXAMPLE 13

2,3-Dihydrobenzo[1,4]dioxine-2-carboxylic acid *N'*-(5-chloro-1*H*-indole-2-carbonyl)hydrazide



To a solution of 5-chloro-1*H*-indole-2-carboxylic acid hydrazide (Preparation 1, 0.50g, 2.39mmol) in DMF (5mL) was added HOBT (0.32g, 2.39mmol), DIPEA (0.83mL, 4.78mmol) and 2,3-dihydrobenzo[1,4]dioxine-2-carboxylic acid (0.43g, 2.39mmol) followed by EDCI (0.55g, 2.87mmol). The reaction mixture was stirred at rt for 16h, poured into water (75mL) and extracted with ethyl acetate (2 x 150mL). The combined organic extracts were washed with HCl (1N, 50mL), NaOH (1N, 50mL) and saturated sodium chloride solution (75mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound. m/z (ES^+) = 372 [$M + H$] $^+$; RT = 3.57min.

The coupling of the appropriate carboxylic acid with 5-chloroindole-2-carboxylic acid hydrazide outlined in EXAMPLE 13, was also employed to prepare the compounds listed in Table 3 below.

Table 3

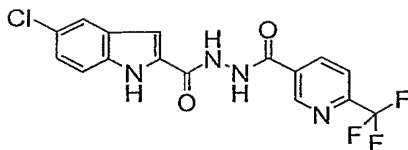
| EX. | Structure | Name | RT (min) | m/z (ES^+) |
|-----|-----------|---|----------|------------------|
| 14 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -(diphenylacetyl)hydrazide | 3.85 | 404 |
| 15 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -(2-benzenesulfonylacetyl)hydrazide | 3.40 | 392 |

| EX. | Structure | Name | RT (min) | m/z (ES ⁺) |
|-----|-----------|---|----------|------------------------|
| 16 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -(2-phenoxyacetyl)hydrazide | 3.48 | 344 |
| 17 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -[2-(5-chlorobenzo[b]thiophen-3-yl)acetyl]hydrazide | 3.70 | 418 |
| 18 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -[2-(4-methoxyphenoxy)acetyl]hydrazide | 3.48 | 374 |
| 19 | | 5-Chloro-1 <i>H</i> -indole-2-carboxylic acid <i>N'</i> -isobutyrylhydrazide | 3.18 | 280 |
| 20 | | 1 <i>H</i> -Benzoimidazole-5-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 2.83 | 354 |
| 21 | | 1 <i>H</i> -Benzotriazole-5-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 3.18 | 355 |
| 22 | | 2,2-Difluorobenzo[1,3]dioxole-5-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 3.66 | 394 |
| 23 | | 8-Methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 3.70 | 398 |
| 24 | | 1 <i>H</i> -Pyrrolo[2,3-c]pyridine-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 2.78 | 354 |
| 25 | | 5-Chloro-1 <i>H</i> -pyrrolo[2,3-c]pyridine-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 3.38 | 389 |
| 26 | | 1,3-Dimethyl-1 <i>H</i> -thieno[2,3-c]pyrazole-5-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 3.41 | 388 |

| EX. | Structure | Name | RT (min) | m/z (ES ⁺) |
|-----|-----------|---|----------|------------------------|
| 27 | | Tetrahydrofuran-3-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 3.15 | 308 |
| 28 | | Tetrahydrofuran-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 3.21 | 308 |
| 29 | | Tetrahydropyran-4-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 3.13 | 322 |
| 30 | | 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 2.87 | 369 |
| 31 | | 2-Amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 2.88 | 383 |
| 32 | | 3-[<i>N'</i> -(5-Chloro-1 <i>H</i> -indole-2-carbonyl)hydrazinocarbonyl]-3,4-dihydro-1 <i>H</i> -isoquinoline-2-carboxylic acid <i>tert</i> -butyl ester | 3.82 | 469 |
| 33 | | {2-[<i>N'</i> -(5-Chloro-1 <i>H</i> -indole-2-carbonyl)hydrazinocarbonyl]-1,2,3,4-tetrahydronaphthalen-2-yl} carbamic acid <i>tert</i> -butyl ester | 3.87 | 483 |
| 34 | | Pyrimidin-5-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 3.09 | 316 |
| 35 | | 2-Methoxyoxazole-5-carboxylic acid <i>N'</i> -(5-chloro-1 <i>H</i> -indole-2-carbonyl)hydrazide | 1.32 | 335 |

EXAMPLE 36

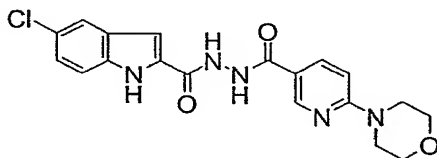
6-Trifluoromethylnicotinic acid *N'*-(5-chloro-1*H*-indole-2-carbonyl)hydrazide



To a solution of 6-(trifluoromethyl)nicotinic acid hydrazide (105mg, 0.51mmol) in DMF (5mL) was added triethylamine (93 μ L, 1.28mmol), 5-chloro-1*H*-indole-2-carboxylic acid (195mg, 0.51mmol), HOBt (69mg, 0.51 mmol) and EDCI (108mg, 0.56mmol). The reaction mixture was allowed to stir at rt for 16h. Water (10mL) was added to the reaction mixture and the title compound was collected by filtration. m/z (ES^+) = 383 [$M + H$] $^+$; RT = 3.53min.

EXAMPLE 37

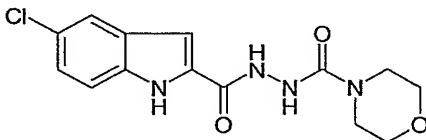
6-Morpholin-4-ylnicotinic acid *N'*-(5-chloro-1*H*-indole-2-carbonyl)hydrazide



To a solution of 6-morpholinonicotinic acid hydrazide (114mg, 0.51mmol) in DMF (5mL) was added triethylamine (93 μ L, 1.28mmol), 5-chloro-1*H*-indole-2-carboxylic acid (195mg, 0.51mmol), HOBt (69mg, 0.51mmol) and EDCI (108mg, 0.56mmol). The reaction mixture was stirred at rt for 16h. Water (10mL) was added to the reaction mixture and the title compound was collected by filtration. m/z (ES^+) = 400 [$M + H$] $^+$; RT = 4.78min.

EXAMPLE 38

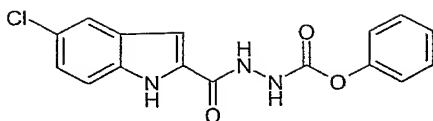
Morpholine-4-carboxylic acid *N'*-(5-chloro-1*H*-indole-2-carbonyl)hydrazide



To a solution of 5-chloro-1*H*-indole-2-carboxylic acid hydrazide (Preparation 1, 0.15g, 0.72mmol) in THF (10mL) was added DIPEA (0.25mL, 1.44mmol) and morpholine-4-carbonyl chloride (84.0mL, 0.72mmol). The reaction mixture was stirred at rt for 4h and concentrated *in vacuo* to give a yellow solid which was dissolved in ethyl acetate (200mL) and THF (25mL). The solution was washed with saturated sodium bicarbonate solution (75mL) and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel (dichloromethane/methanol, 19:1) to give the title compound. m/z (ES^+) 323 [$M + H$] $^+$; RT = 3.12min.

EXAMPLE 39

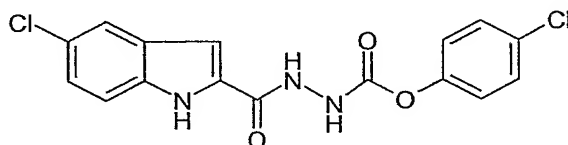
N'-(5-Chloro-1*H*-indole-2-carbonyl)hydrazine carboxylic acid phenyl ester



Triethylamine (39 μ L, 0.28mmol) was added to a mixture of 5-chloroindole-2-carboxylic acid hydrazide (Preparation 1, 50mg, 0.24mmol) and phenyl chloroformate (35 μ L, 0.28mmol) in DCM (2mL) and the mixture was stirred at rt for 2h. A further aliquot of phenyl chloroformate (20 μ L) was added and stirring was continued for a further 1h. The solution was partitioned between ethyl acetate (50mL) and water (50mL) and the organic phase was then washed with HCl (2M, 50mL), dried (MgSO₄) and concentrated *in vacuo*. The solid was triturated with ethyl acetate, collected by filtration, triturated once more with acetonitrile, collected by filtration and dried to give the title compound. δ_H (d₆ DMSO): 7.78 (1H, d), 7.57-7.41 (3H, m), 7.39-7.25 (4H, m), 7.21 (1H, d); RT = 3.98min.

EXAMPLE 40

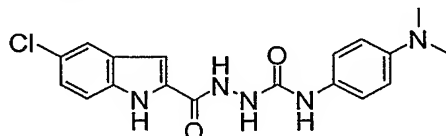
N'-(5-Chloro-1*H*-indole-2-carbonyl)hydrazine carboxylic acid 4-chlorophenyl ester



Triethylamine (39 μ L, 0.28mmol) was added to a mixture of the 5-chloro-1*H*-indole-2-carboxylic acid hydrazide (Preparation 1, 50mg, 0.24mmol) and *p*-chlorophenyl chloroformate (39 μ L, 0.28mmol) in DCM (2mL) and the mixture was stirred at rt for 2h. A further aliquot of *p*-chlorophenyl chloroformate (20 μ L) was added and stirring was continued for a further 1h. The solution was partitioned between ethyl acetate (50mL) and water (50mL) and the organic phase was then washed with HCl (2M, 50mL), dried over MgSO₄ and concentrated *in vacuo*. The solid was triturated with ethyl acetate, collected by filtration, triturated once more with acetonitrile, collected by filtration and dried to give the title compound. δ_H (d₆ DMSO): 7.78 (1H, d), 7.59 (2H, d), 7.48 (1H, d), 7.39 (2H, d), 7.28 (1H, d), 7.21 (1H, d); RT = 4.15min.

EXAMPLE 41

5-Chloro-1*H*-indole-2-carboxylic acid *N'*-(4-(*N,N*-dimethylamino)phenylaminocarbonyl)hydrazide



To a suspension of 5-chloro-1*H*-indole-2-carboxylic acid hydrazide (Preparation 1, 100mg, 0.48mmol) in toluene (5mL) was added 4-(dimethylamino)phenylisocyanate (77mg, 0.48mmol) and the reaction mixture was stirred at 80°C for 48h. The reaction mixture was cooled and filtered. The solid was washed with isohexane to give the title compound. m/z (ES⁺) = 372 [$M + H$]⁺; RT = 3.65min.

The biological activity of the compounds of the invention may be tested in the following assay systems:

In vitro GP activity

Materials:

α -D-Glucose-1-Phosphate (disodium salt), Glycogen, D-Glucose, Malachite Green Hydrochloride, Ammonium Molybdate tetrahydrate, BSA, HEPES and rabbit muscle phosphorylase α (P1261) were purchased from Sigma. All other reagents were analytical grade.

Method

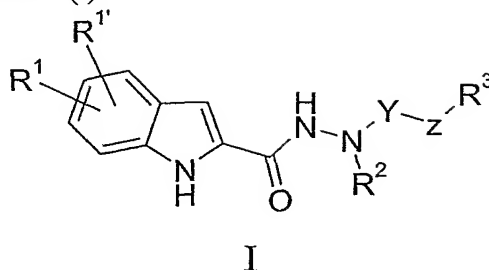
Glycogen phosphorylase assay *in vitro*:

An assay for glycogen phosphorylase activity in the reverse direction was developed based on the method described by Engers *et al.*, *Can. J. Biochem.*, 1970, 48, 746-754]. Rabbit muscle glycogen phosphorylase α (Sigma) was reconstituted at a stock concentration of 100 μ g/mL in 25mM Tris/HCl. The pH was measured in a 96-well plate in a final volume of 100 μ L containing 50mM Hepes pH 7.2, 7.5mM glucose, 0.5mM glucose-1-phosphate and 1mg/mL glycogen. After incubation at 30°C for 30min, the inorganic phosphate released from glucose-1-phosphate was measured by the addition of 150 μ L of malachite green/molybdate solution prepared as follows: 5mL of 4.2% ammonium molybdate in 4N HCl, 15mL of 0.045% malachite green, 50 μ L of Tween 20. Following a 30 min incubation at rt, the absorbance was measured at 620nm. For IC₅₀ determination, 10 μ L of a serial dilution of compound (100 μ M to 0.004 μ M) in DMSO was added to each reaction in duplicate with the equivalent concentration of DMSO added to the control uninhibited reaction. Dose response curves were then obtained by plotting % inhibition versus log₁₀ compound concentration. IC₅₀ is defined as the concentration of compound achieving 50% inhibition under the assay conditions described.

Examples of compounds of the present invention demonstrated efficacy in the above assay with IC₅₀ results in the range of better than 100 μ M.

CLAIMS:

1. A compound of formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

Y is -C(O)-, -S(O)₂-, or -C(NH)-;

Z is C₁₋₄alkylene, oxygen, -(CH₂)_mO-, -O(CH₂)_m-, -NR-, -(CH₂)_mNR-, -NR(CH₂)_m-, -(CH₂)_mS(O)₂-, or a bond;

m is 1, 2, 3, or 4;

R is C₀₋₄alkyl, C₀₋₄alkylaryl, or C₀₋₄alkylheteroaryl;

R¹ and R^{1'} are each independently, halogen, hydroxy, cyano, C₀₋₄alkyl, C₁₋₄alkoxy, fluoromethyl, difluoromethyl, trifluoromethyl, ethenyl, or ethynyl;

R² is C₀₋₄alkyl, COOR⁶, COR⁶, C₁₋₄alkoxyC₁₋₄alkyl-, hydroxyC₁₋₄alkyl-, cycloalkylC₀₋₄alkyl-, arylC₀₋₄alkyl-, or hetarylC₀₋₄alkyl-, wherein any of the aryl or hetaryl rings are optionally substituted with 1-2 independent halogen, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, -N(C₀₋₄alkyl)(C₀₋₄alkyl), -SO₂C₁₋₄alkyl, -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents;

R³ is hydrogen, -COOC₀₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkyl, arylC₁₋₄alkylthio-, -C₀₋₄alkylaryl, -C₀₋₄alkylhetaryl, -C₀₋₄alkylcycloalkyl, or -C₀₋₄alkylheterocyclyl, wherein any of the rings is optionally substituted with 1-3 independent halogen, cyano, C₁₋₄alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, -C₀₋₄alkylNHC(O)O(C₁₋₄alkyl), -C₀₋₄alkylNR⁷R⁸, -C(O)R⁹, C₁₋₄alkoxyC₀₋₄alkyl-, -COOC₀₋₄alkyl, -C₀₋₄alkylNHC(O)R⁹, -C₀₋₄alkylC(O)N(R¹⁰)₂, -C₁₋₄alkoxyC₁₋₄alkoxy, hydroxyC₀₋₄alkyl-, -NHSO₂R¹⁰, -SO₂(C₁₋₄alkyl), -SO₂NR¹¹R¹², 5- to 6-membered heterocyclyl, phenylC₀₋₂alkoxy, or phenylC₀₋₂alkyl substituents, wherein phenyl is optionally substituted with 1-2 independent halogen, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, -N(C₀₋₄alkyl)(C₀₋₄alkyl), -SO₂C₁₋₄alkyl, -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), hydroxy, fluoromethyl, difluoromethyl, or trifluoromethyl substituents, or two bonds on a ring carbon of the heterocyclyl group optionally can form an oxo (=O) substituent;

or R³ is -NR⁴(-C₀₋₄alkylR⁵);

R⁴ is C₀₋₃alkyl, -C₂₋₃alkyl-NR⁷R⁸, C₃₋₆cycloalkyl optionally substituted by hydroxyC₀₋₄alkyl- further optionally substituted by hydroxy, C₁₋₂alkoxyC₂₋₄alkyl-, or C₁₋₂alkyl-S(O)_n-C₂₋₃alkyl-;

n is 0, 1, or 2;

R⁵ is hydrogen, hydroxyC₂₋₃alkyl-, C₁₋₂alkoxyC₀₋₄alkyl-, or aryl, hetaryl, or heterocyclyl;

wherein a heterocyclic nitrogen-containing R⁵ ring optionally is mono-substituted on the ring nitrogen with C₁₋₄alkyl, benzyl, benzoyl, C₁₋₄alkyl-C(O)-, -SO₂C₁₋₄alkyl, -SO₂N(C₀₋₄alkyl)(C₀₋₄alkyl), C₁₋₄alkoxycarbonyl, or aryl(C₁₋₄alkoxy)carbonyl; and wherein the R⁵ rings are

optionally mono-substituted on a ring carbon with halogen, cyano, C₁₋₄alkyl-C(O)-, C₁₋₄alkyl-SO₂-, C₁₋₄alkyl, C₁₋₄alkoxy, hydroxy, -N(C₀₋₄alkyl)(C₀₋₄alkyl), hydroxyc₀₋₄alkyl-, or C₀₋₄alkylcarbamoyl-, provided that no quaternised nitrogen is included; or two bonds on a ring carbon of the heterocycle optionally can form an oxo (=O) substituent;

R⁶ is C₁₋₄alkyl, aryl, or hetaryl;

R⁷ and R⁸ are independently C₀₋₄alkyl, C₃₋₆cycloalkyl, or CO(C₁₋₄alkyl);

R⁹ is C₁₋₄alkyl, or C₃₋₆cycloalkyl;

R¹⁰ is C₀₋₄alkyl, or C₃₋₆cycloalkyl; and

R¹¹ and R¹² are independently C₀₋₄alkyl or together with the nitrogen to which they are attached may form a 4- to 6-membered heterocycle;

provided there are no nitrogen-oxygen, nitrogen-nitrogen, oxygen-oxygen or nitrogen-halogen bonds in the grouping -Y-Z-R³; and

provided that when -Y-Z- represents -C(O)-, -C(NH)-, -C(O)-C₁₋₄alkylene, -C(NH)-C₁₋₄alkylene, -C(O)-NR-, -C(NH)-NR-, -C(O)-(CH₂)_mNR-, or -C(NH)-(CH₂)_mNR-, then R³ is not optionally substituted C₃₋₁₀cycloalkyl, C₅₋₁₀cycloalkenyl, phenyl, naphthyl, pyridyl, pyrazinyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, furanyl, thiophenyl, pyrrolyl, pyrrolidinyl, piperidinyl, indolyl, benzo[1,3]dioxol, thieno[2,3-b]pyrrolyl, or thieno[3,2-b]pyrrolyl.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein Y is -C(O)- or -S(O)₂-.
3. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Z is C₁₋₄alkylene, oxygen, -(CH₂)_mO-, -NR- or a bond.
4. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein Y is -C(O)-.
5. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein Y is -S(O)₂-.
6. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R¹ and R^{1'} are each independently, hydrogen or halogen.
7. A compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein one of R¹ and R^{1'} is hydrogen and the other is 5-chloro.
8. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R² is hydrogen.
9. A compound of formula (I) as defined in any one of Examples 1 to 41, or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.
11. A method for the treatment of a disease or condition in which glycogen phosphorylase plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof.
12. A method for the treatment of hyperglycemia or diabetes comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof.
13. A method for the prevention of diabetes in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance comprising a step of administering to a subject in need thereof an effective prophylactic amount of a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof.
14. A method for the treatment of hypercholesterolemia, hyperinsulinemia, hyperlipidemia, hypertension, atherosclerosis or tissue ischemia, or achieving cardioprotection or inhibition of abnormal cell growth, comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof.